REMARKS

Claims 1-6 are pending in the present application. Claims 1-5 are rejected. Claims 1 and 4-6 are herein amended.

Applicants' Response to Objections to the Specification

The specification is objected to for failing to contain reference to the prior application. This application was based on Provisional Application No. 60/414,412. Accordingly, Applicants herein amend the specification in order to insert this cross-reference. Favorable reconsideration is respectfully requested.

Applicant's Response to Claim Rejections under 35 U.S.C. §112

Claims 1-5 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The Office Action rejects the application on based on several issues of enablement. Each is discussed below.

"treating" vs. "preventing"

It is the position of the Office Action that that the specification does not disclose *preventing* kidney disease by administration of PAR-2 ligands. The Office Action states that "prevent" is interpreted as meaning that an activity will not occur, i.e., kidney disease will not

occur. In other words, it appears to be the position of the Office Action that the specification does not enable one skilled in the art to ensure that the relevant kidney diseases do not occur at all, rather than treat them once they have occurred.

In response, Applicants herein amend the claims to remove the recitation of "prevention." Accordingly, the pending claims now recite only "treatment." Additionally, withdrawn claim 6 has been similarly amended. Finally, Applicants note that claims 4 and 5 are also amended in order to improve the form of the claims.

PAR-2 plays an important role in kidney diseases

The Office Action states that the specification teaches adding the mouse SLIGRL peptide to animals with an experimentally induced nephritis. However, the Office Action states that there is no evidence from the literature or the specification that PAR-2 plays a role in any kidney diseases, including the one which was experimentally induced in the Examples.

The Office Action appears to question whether the experimentally induced nephritis was produced by a mechanism involving PAR-2. The Office Action then states that "the animals in which an experimental glomerulonephritis was generated were PAR-2 knockouts." The Office Action then concludes that PAR-2 does not have a role in the glomerulonephritis, since knockout mice still developed the glomerulonephritis.

In response, Applicants respectfully submit that the Office Action did not understand the experimental data. The knockout mice were only used to confirm the role of PAR-2 in the generation of the glomerulonephritis. As illustrated in Figure 1, when anti-GBM antibodies were

administered, wildtype mice generated relatively lower amounts of albumin in their urine, while knockout mice generated exponentially higher levels of albumin. The role of PAR-2 in glomerulonephritis is also confirmed by the experimental data of Figures 2(a), 2(b), 3(a) and 3(b). These Figures illustrate that the knockout mice had much higher levels of precipitation of PAS-positive substances and damage to Bowman's capsules, as compared to wildtype mice. These data strongly suggest that the *lack* of a functional PAR-2 gene leads to a significant increase in glomerulonephritis-related symptoms when nephritis is induced, or that PAR-2 is involved to suppress or inhibit the aggravation of glomerulonephritis caused by anti-GBM antibodies.

It appears that the Office Action fails to appreciate that the experiments illustrated in Figures 4 and 5 were conducted on wildtype mice. The Office Action states that there is a "lack of working examples in which a glomerulonephritis was treated in animals that had functional PAR-2 receptors." In response, Applicants respectfully indicate that both Examples 3 and 4, illustrated in Figures 4 and 5, were performed on *wildtype* mice, having functioning PAR-2 genes, encoding functional PAR-2 receptors. In these experiments using wildtype mice, the treatment with a PAR-2 activator resulted in greatly lowered levels of albumin, as compared to the control group and the conventionally treated (prednisolone-administered) group. This indicates that these ligands are successful for treating experimentally induced glomerulonephritis.

Additionally, the Office Action states that Rondeau has pointed out that PAR-2 knockout animals, if they survive early development, are phenotypically-normal, and states that this indicates that PAR-2 plays a minor role in adult kidney physiology. The relevant passage of

Rondeau states that "Invalidation of these genes [referring to PAR-1, PAR-2, PAR-3 and PAR-4] has been performed in mice, and mild or no phenotype was observed in living KO animals, suggesting a compensatory function of one receptor by others, or a minor effect of these receptors in normal mice." See Rondeau, page 1529, paragraph 4, last five lines.

It is unclear what Rondeau regards as "phenotype." However, it is clear from the experimental data provided in Figures 1-3 that the PAR-2 gene has a significant effect on at least glomerulonephritis. Furthermore, the documents submitted in the Information Disclosure Statements of September 30, 2003 and May 24, 2005 all discuss the importance of PAR-2 with respect to a variety of conditions.

Specifically, Applicants refer to the Gui reference, which was filed in the September 30, 2003 Information Disclosure Statement and published after the priority date of the application. The Gui reference shows that PAR-2 activating peptide (SLIGRL-NH2) caused the increase of renal perfusion flow rate (RPF) and glomerular filtration rate (GFR) in isolated perfused kidney that has been prereduced by angiotensin II. Gui also showed that thrombin, which activates PAR-1, reduces GFR and RPF, Thus, Gui teaches that PAR-2 has a protective activity with respect to the kidney. Therefore, in view of the above comments, Applicants respectfully submit that the discussion of Rondeau is not applicable to the present invention.

The experimental data may be reasonably extrapolated to humans

The Office Action also states that no attempt was made to associate the experimental data with naturally occurring kidney diseases in human patients with PAR-2. On a similar note, the Office Action states that it cannot be generalized that the experimental results in mice are relevant to humans.

In response, Applicants respectfully submit that it is generally acknowledged by those skilled in the art that some mammals such as OLETF-rat or others are used as non-human model animals for exploring drugs to be used for humans. For example, with reference to kidney diseases, Taniguchi, et al. (enclosed herewith) discloses that crescentic-type anti-GBM nephritis rats are used to investigate the antinephritic effect of methylpredonisolone suleptanate, and that methylpredonisolone suleptanate has a marked antinephritic action. The results shown in Taniguchi have been affirmed by Zheng, et al. (enclosed herewith), which shows that methylpredonisolone actually treats human crescentic glomerulonephritis. See abstracts.

In view of the above, Applicants respectfully submit that it is acknowledged by those skilled in the art that rats can be used as human model animals and that the observed results can be extrapolated to humans.

The method of administration of peptides disclosed in the specification is known to be reliable

Finally, the Office Action questions the reliability of the administration of peptides, as compared to more stable non-peptidic small molecules. The Office Action states that due to the

number of proteases in many tissues, it is unclear that the peptide would survive intact to pass to the kidney to have an effect.

In response, Applicants respectfully submit that it is common knowledge that there are a number of polypeptide drugs such as insulin, interferon, tissue-plasminogen activator or others, which are approved as drugs to be intravenously administered. The specification of the instant application explicitly and sufficiently discloses that the intravenous administration of SLIGRL works on rats of which blood contains proteases. See Examples.

In summary

In view of the above remarks and the attached documentary evidence, Applicants respectfully submit that contrary the Office Action's interpretation of Rondeau, PAR-2 is a key actor in adult kidney physiology. Applicants further submit that the induced glomerulonephritis experiment in mice is a sufficient model for a variety of naturally occurring kidney diseases in humans. Finally, Applicants also respectfully submit that peptides are a reliable method of treatment. Accordingly, Applicants respectfully submit that for at least the above reasons, all of claims 1-5 comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Favorable reconsideration is respectfully requested.

Claims 1-5 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time of filing.

It is the position of the Office Action that the specification does not provide a sufficient written description to show that the inventor had possession of the claimed invention at the time the application was filed.

SLIGRL and ASKH95 are sufficient models for PAR-2 activators

Specifically, it is the position of the Office Action that the specification only teaches the use of mouse PAR-2 ligand polypeptide SLIGRL. The Office Action states that "the description of one polypeptide is not adequate written description of an entire genus of functionally equivalent polypeptides or other non-peptide ligands." The Office Action also states that the specification does not teach functional or structural characteristics of all PAR-2 activating agents used for the claimed methods. However, it is noted that the specification also discloses the use of SLIGKV and ASKH95. See page 15, lines 4-15. The experimental data utilizes both SLIGRL and ASKH95.

In response, Applicants respectfully submit that the ligands SLIGRL and ASKH95 are sufficient models for PAR-2 activators generally. Such PAR-2 activators include PAR-2 ligands generally, PAR-2 ligand derivatives, trypsin, tryptase, tissue factor/VIIa factor, Xa factor, acrosin or trypsin-like serine protease.

The polypeptide of SLIGRL is a natural ligand to mouse PAR-2, which activates PAR-2. ASKH95 is a chemically modified human PAR-2 ligand of SLIGKV. SLIGRL or SLIGKV are produced from PAR-2 itself by the digestion of PAR-2 with proteolytic polypeptides such as those recited in claim 5. Such proteolytic polypeptides are also acknowledged as PAR-2 activating agents because they activate PAR-2 via production of SLIGRL. See "Background of Invention."

The functional characteristics of PAR-2 activating agents should therefore be understood as "PAR-2 activating activity" which is quite apparent from the Examples. Thus, Applicants respectfully submit that SLIGRL and ASKH95 are sufficient models for the broad genus of PAR-2 activators, in view of the above-discussed mechanisms of how SLIGRL is produced and how it works.

The PAR-2 activators recited in claim 5 are in fact PAR-2 activators

Additionally, the Office Action states that "the recited PAR-2 ligands in claim 5 are better known as PAR-1 ligands (Rondeau et al, 2001) and have not been confirmed as PAR-2 ligands." In response, Applicants respectfully submit that Rondeau contains no disclosure to show that the PAR-2 ligands in claim 5 are better known as PAR-1 ligands. Actually, Rondeau only discloses that thrombin and PAR-1 agonist peptide SFLLRN activate PAR-1. There is no suggestion or disclosure in Rondeau with regard to tryptase, tissue factor/VIIIa factor, Xa factor acrosin or trypsin-like serine protease. Additionally, Applicants note that they have clearly described, with citing references, that the proteins recited in claim 5 are known as PAR-2 activators.

Therefore, in view of the above, Applicants respectfully submit that SLIGRL and ASKH95 are sufficient models for the broad genus of PAR-2 activators. Furthermore, Applicants respectfully submit that the PAR-2 activators recited in claim 5 are in fact PAR-2 activators. Accordingly, Applicants respectfully submit that all of claims 1-5 comply with the written description requirement of 35 U.S.C. §112, first paragraph. Favorable reconsideration is respectfully requested.

For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

Should the Examiner deem that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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Enclosures: Petition for Extension of Time
Taniguchi, et al. "Marked Antinephritic Action and Less Adverse Effects of Methylprednisolone Suleptanate by Intermittent Administration in Rats." *Jpn. J. Pharmacol.*, 64: 79-88, 1994.
Zheng, et al. "Effects of methylpredonisolone and cyclophosphamide pulse therapy on renal infiltrating cells in patients with crescentic glomerulonephritis." *Chinese Medical Journal*, 110 (3), 206-209, 1997.